SPECIAL ISSUE ARTICLE

Uncommon Neonatal Skin Lesions

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ABSTRACT

Certain rashes and cutaneous lesions in a newborn can be clues to more concerning diseases and conditions if recognized and evaluated promptly. Langerhans cell histiocytosis, cutaneous forms of cancer (such as leukemia cutis, neuroblastoma, and rhabdomyosarcoma), developmental abnormalities such as neural tube or spinal dysraphism, and aplasia cutis congenita, nutritional deficiency, and immunodeficiency all have a range of cutaneous findings that will be reviewed herein to guide diagnosis and management. **[*Pediatr Ann*. 2019;48(1):e30-e35.]**

Many neonatal skin rashes are innocuous, but particular cutaneous signs may point to more serious underlying disorders. It is important that pediatricians and dermatologists be able to recognize rashes and lesions that, together with systemic manifestations, may explain concerning neonatal conditions. This article discusses less commonly seen but extremely important neonatal skin lesions. This article covers cutaneous signs of cancer, developmental abnormalities of the newborn, including signs and symptoms of neural tube and spinal dysraphism, signs of nutritional deficiency, and markers of primary immunodeficiency.[1,2]

CUTANEOUS SIGNS OF CANCER

Certain neonatal cancers can present at birth and skin findings may be the presenting sign. Typically, patients present with erythematous to violaceous papules and nodules. When violaceous lesions are widely disseminated, it leads to the classic "blueberry muffin" baby. This term was initially coined in the 1960s by pediatricians to describe the cutaneous manifestations of newborns infected with rubella; however, the differential diagnosis has expanded beyond even the congenital TORCH (Toxoplasmosis, Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, and Herpes) infections to include severe hemolysis and early onset neonatal malignancies. Blueberry muffin lesions due to a neoplastic or infiltrative process are often larger, fewer in number, and firmer to palpation than the infectious causes, which will not be discussed in this article.

The presence of blueberry muffin lesions at birth indicates bone marrow dysfunction. In normal development, extramedullary hematopoiesis occurs in several organs, including the dermis. Dermal erythropoiesis can occur in the setting of hematologic dyscrasias such as Rh incompatibility, maternofetal ABO blood type incompatibility, spherocytosis, and twin-twin transfusion syndrome. Patients will present with nonblanching papules and nodules secondary to compensatory extramedullary hematopoiesis from severe anemia.[3]

Leukemia Cutis

Congenital leukemia cutis is a rare manifestation of leukemia occurring in approximately 25% to 30% of patients with congenital leukemia but representing less than 1% of all childhood leukemias.[4,5] It can be associated with a variety of types of childhood leukemias, including acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphoblastic leukemia, and chronic myeloid leukemia.

Although the cutaneous infiltration of leukemic cells presents with various phenotypes, including macules, papules, plaques, nodules, bullous lesions, and seborrheic-dermatitis–like lesions, the most characteristic lesions include red-brown to violaceous papules or nodules, many of which are often purpuric.[2] Congenital leukemia cutis is often associated with anemia, leukocytosis, and hepatosplenomegaly.

Thorough testing must be performed including a skin biopsy, serology, peripheral smear, bone marrow aspirate, and cytogenetics. Although

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most cases of congenital leukemia cutis portend a poor prognosis, with a 20% survival by age 2 years, there are a few case reports of spontaneous remission.[5-7]

Neuroblastoma

Neuroblastoma, an embryonal tumor arising from the sympathetic nervous system, is one of the most common neonatal malignancies.[8] Infants usually present with abdominal masses originating from the adrenal gland, visceral ganglia, or sympathetic chain. Nevertheless, cutaneous metastases may be the presenting signs of neuroblastoma, classically falling into the spectrum of blueberry muffin lesions with firm blue-to-purple papules and nodules. The lesions characteristically blanch on palpation resulting in a halo of erythema secondary to the production of catecholamines by the tumor. Ocular signs include periorbital ecchymosis ("raccoon eyes") and heterochromia iridis secondary to involvement of the ophthalmic sympathetic nerve.

When neuroblastoma is suspected, skin biopsy with histologic evaluation, immunophenotyping, and genetic analysis may be indicated. Initial evaluation must include urine and serum catecholamines, computed tomography (CT) or magnetic resonance imaging (MRI), bone marrow aspirate, and biopsy as well as iodine-123 metaiodobenzylguanidine scintigraphy. The natural history of neuroblastoma is quite variable with reports of spontaneous remission to development of extensive metastatic disease with associated mortality.[1] When occurring in the neonatal period, cutaneous metastases of neuroblastoma confer a more favorable prognosis as compared to older patients with metastatic disease.[9]

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a soft-tissue neoplasm of skeletal muscle origin and is one of the most common malignant solid tumors in childhood. The two histologic subtypes are embryonal RMS and alveolar RMS. Clinically, patients present with asymptomatic rapidly expanding masses of the head and neck or genitourinary tract. Congenital alveolar rhabdomyosarcoma is a rare variant with more than 50% of patients presenting with multiple cutaneous metastases described as soft cherry red to firm violaceous nodules.[10] The prognosis is less favorable for infants compared to older children.[11,12]

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) represents a disease spectrum characterized by infiltration of histiocytes within blood and tissues. LCH is classified by the extent of involvement (single versus multiple organ systems) and involvement of certain high-risk organs (liver, spleen, or bone marrow).[13,14]

The most common neonatal cutaneous presentation involves red brown papules and nodules, often with crust, hemorrhage, erosions, petechiae, or vesicopustular lesions that favor the scalp, trunk, diaper area, and skin folds.[1] Erythematous scaly eruptions in a seborrheic distribution are common. A "blueberry muffin baby" presentation has also been reported.

When LCH presents outside of the skin, the other organs involved may include the bones, lymph nodes, liver, spleen, lungs, gastrointestinal system, thymus, bone marrow, kidneys, and central nervous system.

Patients with suspected LCH should undergo a complete physical examination, laboratory evaluation (including complete blood count, serum electrolytes and serum osmolality, liver function tests), urine osmolality, skin biopsy, skeletal survey, and a chest X-ray. An oncology referral for possible bone marrow aspiration or biopsy is advised.

The prognosis depends upon organs involved and to a lesser extent, the age of the patient. Involvement of the liver, spleen, or bone marrow portends a worse prognosis as does younger age.[2] LCH limited to the skin has a favorable prognosis, and a careful watchful waiting approach can be employed by observing children to ensure they do not develop extracutaneous lesions months to years later. The 5-year survival rate of patients with single-organ cutaneous disease approaches 83% to 88%, whereas multisystem disease especially with initial liver or spleen involvement has a 25% 5-year survival rate.[13]

DEVELOPMENTAL ABNORMALITIES

Neural tube and spinal dysraphism occur secondary to abnormal fusion of the neural tube during embryogenesis. The skin and the nervous system share an ectodermal origin and thus the skin often serves as a marker for underlying malformations. Although open neural tube defects can often be diagnosed in-utero, closed or occult defects often only present with cutaneous stigmata, which are often innocuous appearing.

Cutaneous Signs of Neural Tube Dysraphism

Faulty fusion of the neural tube, which closes in a segmental, noncontiguous pattern, can present with cutaneous findings. Some findings are quite large and more likely to raise concern, while others are smaller and harder to appreciate.[15]

Cutaneous neural heterotopia refers to congenital herniation of intracranial structures into the subcutaneous tissue or dermis of the skin. Collectively termed

"cephaloceles," these can manifest as an encephalocele (herniation of glial and meningeal tissue) or a meningocele (herniation of only meninges and cerebral spinal fluid). Cephaloceles present as soft, compressible nodules that occur at any point along, or just lateral to, the midline from the nasal root to the sacral spine. The lesion will grow in size with increases in intracranial pressure from crying or straining and can be a useful diagnostic feature. They may be covered with normal skin or have a blue or glistening appearance. An overlying capillary malformation or a peripheral ring of coarse, dark hair ("hair collar sign") is extremely concerning for dysraphism.[16] Given the strong association of underlying cranial dysraphism with these midline lesions, MRI prior to biopsy or surgical excision is required.

A nasal glioma is a mass of ectopic brain tissue that presents as a firm, noncompressible skin-colored to blue-red mass protruding from the nasal bridge or nasal cavity. Unlike cephaloceles, there is no intracranial communication. They are often misdiagnosed as hemangiomas, although do not undergo a proliferative or involutional phase, which can help distinguish the two entities. Surgical excision is required to avoid respiratory distress and correct the deformity after imaging is performed.[14]

Dermoid cysts and sinuses represent epithelial-lined tracts along embryonic fusion lines and can contain epidermal and dermal components. Although congenital, they often go unnoticed until they enlarge or become inflamed or infected. Dermoid cysts are firm, noncompressible skin-colored to blue subcutaneous nodules that can occur anywhere along the face, scalp, or spinal axis. They most commonly occur on the upper lateral forehead (lateral eyebrow), submental region, or overlying the anterior fontanelle. When a dermoid cyst occurs in the nasal midline (glabella, nasal dorsum and columella), there can be potential for intracranial connection. A dermoid sinus is a midline 1- to 5-mm tract connecting a dermoid cyst to the epidermis, which can indicate a higher likelihood for intracranial communication (50% vs 25%).[14] Direct communication with the central nervous system can serve as a nidus for bacteria, often causing recurrent meningitis.[17] All midline dermoid cysts require radiographic imaging (CT and/or MRI) prior to surgical intervention; however, those off the midline do not require imaging or treatment unless desired.[14]

Cutaneous Signs of Spinal Dysraphism

Occult spinal dysraphism can have associated long-term sequelae and irreversible neurologic complications. Hypertrichosis, dimples (>2.5 cm from the anal verge and ≥5mm in size), acrochordons, pseudotails, true tails, lipomas, hemangiomas (>2.5cm),[18] dermoid cysts or sinuses, aplasia cutis, gluteal cleft deviation, and scars in the lumbosacral area are reported with spinal dysraphism. If there are two or more cutaneous lesions occurring along the spinal axis, the risk increases from 8% to 61%.[19] Lipomas with other lesions have the strongest association and have an increased risk even when isolated.[20]

Prior to ossification of the vertebrae (infants age <3 months), ultrasound is an inexpensive screening tool but has low sensitivity, which makes it unreliable.[2] MRI is the diagnostic modality of choice.[18]

Aplasia Cutis Congenita

Aplasia cutis congenita (ACC) is characterized by localized or widespread absence of the skin, including epidermis, dermis, and sometimes the subcutaneous tissues. The clinical appearance ranges from a solitary erosion or ulcer to a glistening thin membrane (membranous ACC) at birth. ACC is most commonly found on the scalp near a hair whorl but may be seen on the face, trunk, or extremities. Especially when accompanied by a hair collar sign, it may indicate an underlying cranial dysraphism. In the case of membranous ACC, imaging studies are necessary to assess for underlying bony, vascular, or brain anomalies.[2] Most small lesions do not require intervention and will flatten and heal with an atrophic scar. Rare cases require grafting to prevent complications related to prolonged healing or dural defects such as sagittal sinus thrombosis and meningitis.[1]

The etiology of ACC is largely unknown. It is thought that rather than having one underlying cause, it is a clinical finding that reflects an abnormality in skin development that can result from a variety of events in-utero. Although it is generally an isolated physical finding or can be inherited as an isolated defect, it can present in the setting of other anomalies including Adams-Oliver syndrome, epidermolysis bullosa, trisomy 13, placental insufficiency, birth trauma, intrauterine infections (ie, herpes simplex virus and varicella zoster virus) and certain drugs used during pregnancy such as methimazole.[21]

SIGNS OF NUTRITIONAL DEFICIENCY

Malnutrition and nutritional deficiencies can result in multisystem disorders and the skin may be a clue to the diagnosis. Nutrients include macronutrients (carbohydrates, protein, and fat) and micronutrients (vitamins and minerals). Nutritional deficiencies are often seen in countries with low income because of insufficient food intake, but it can also been seen in countries with high income associated with various primary or secondary causes including psychiatric disorders (such as anorexia

TABLE 1.

Cutaneous Manifestations of Immunodeficiency

Disorder	Inheritance	Gene or Mutation	Infectious Manifestations	Systemic Manifestations	Cutaneous Manifestations
Severe combined immunodeficiency	AR XLR	*ADA*, *IL2RG*, *IL7R*, *JAK3*	Bacterial, viral, fungal, and protozoan infections	Diarrhea, failure to thrive, pneumonia	Seborrheic dermatitis, morbilliform eruptions, erythroderma, GVHD (rare)
Omenn syndrome	AR	*RAG1*, *RAG2*	Bacterial, viral, and fungal infections	Lymphadenopathy, hepatosplenomegaly, failure to thrive, elevated IgE, eosinophilia	Eczematous dermatitis, erythroderma, alopecia
DiGeorge syndrome	AD	22q11 microdeletion	Fungal and viral infections	Thymic aplasia/hypoplasia, cardiac anomalies, hypoparathyroidism, dysmorphic facies (low set ears, short philtrum, micrognathia, cleft palate)	Eczematous dermatitis, morbilliform rash, granulomatous dermatitis, mucocutaneous candidiasis, erythroderma, GVHD
Chronic granulomatous disease	XLR AR	Mutations in subunits of NADPH oxidase complex	Bacterial (*Staphylococcus aureus*, *Klebsiellosis spp.*, *Serrati marcescens*) and fungal (*Candida spp.*, *Aspergillus spp.*) infections	Pulmonary granulomas/ infections, hepatic abscesses, hepatosplenomegaly	Abscesses, granulomas, lupus erythematosus-like skin lesions (female carriers, affected patients), oral aphthous-like ulcers, Sweet syndrome-like lesions
Hyperimmunoglobulin E syndrome	AD	*STAT3*	Bacterial and fungal infections	Sinopulmonary infections, elevated IgE, bone fractures, scoliosis, dental abnormalities	Neonatal papulopustular eruption and mucocutaneous candidiasis, severe eczematous dermatitis, abscesses
DOCK8 deficiency	AR HIES	*DOCK8*	Bacterial (*S. aureus*), viral (molluscum, HSV, CMV), and fungal (*Candida spp.*) infections	Elevated IgE, vasculitis, anemia, thrombocytopenia, malignancy (cutaneous/mucosal SCC, lymphoma)	Severe eczematous dermatitis, mucocutaneous candidiasis
Wiscott-Aldrich syndrome	XLD	*WAS*	Bacterial and viral infections	Thrombocytopenia, IgE-mediated allergy, asthma, lymphoreticular malignancy (non-Hodgkin's lymphoma)	Bleeding, petechiae, purpura, vasculitis, eczematous dermatitis, urticaria

Abbreviations: AD, autosomal dominant; ADA, adenosine deaminase; AR, autosomal recessive, CMV, cytomegalovirus; DOCK, dedicator of cytokinesis; GVHD, graft-versus-host-disease; HIES, Hyper-IgE syndrome; HSV, herpes simplex virus; IG, immunoglobin; NADPH, nicotinomide adenine dinucleotide phosphate; RAG, recombinase-activating gene; SCC, squamous cell carcinoma; STAT, signal transducer and activator of transcription; XLD, X-linked dominant; WAS,Wiskott-Aldrich syndrome; XLR, X-linked recessive.
Adapted from references 27 to 36.

nervosa) or medical issues related to malabsorption.[22] Many of the cutaneous symptoms are due to disruption in epidermal maturation, resulting in xerosis and epidermal atrophy, and decreased protein production with subsequent dermal atrophy and muscle wasting.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is an acquired or inherited form of zinc deficiency that manifests with rash, irritability, and diarrhea. The disease manifests within several days to weeks of birth in infants who are bottle-fed and shortly after weaning if breast-fed. The classic inherited form is due

to a mutation in a gene encoding an intestinal zinc transporter, *SLC39A4*; however, there are reports of zinc deficiency in babies who are breast-fed by mothers with inadequate zinc secretion (maternal mutation in *SLC30A2*).[23] Additionally, zinc deficiency can occur in patients receiving hyperalimentation without adequate zinc supplementation or in patients with poor zinc absorption secondary to cystic fibrosis, celiac, or Crohn's disease.[24]

Within the first few months of life, sharply demarcated erythema, scale crusts, erosions, or vesicles localized to perioral, acral, and perineal sites develop. Alopecia, conjunctivitis, foul-smelling diarrhea, recurrent candidal or bacterial infections as well as irritability or listlessness may occur.

Low serum zinc levels (<50 mcg/dL) and alkaline phosphatase levels point toward the diagnosis.[1] Blood samples should be collected in sterile acid-washed glass tubes as zinc often contaminates usual glass tubes and stoppers. Testing a mother's breast milk for its zinc concentration can be considered if clinical suspicion is high. Supplementation with zinc leads to a rapid and dramatic improvement in systemic and cutaneous manifestations, with skin findings resolving within days.[25]

Biotin deficiency and certain organicacidurias such as methylmalonic acidemia, proprionic acidemia, glutaric aciduria type 1, maple syrup urine disease, ornithine transcarbamylase deficiency, citrullinemia, and Hartnup disease can present with similar clinical features to acrodermatitis enteropathica.

Other Disorders of Nutritional Deficiency

Kwashiorkor is a severe and acute form of protein deficiency that manifests with hypoalbuminemia, edema, and dermatosis. Although classically seen in developing countries, weaning from breast milk, avoiding food groups due to food allergy, or child abuse are reasons this can occur in more developed countries.[26] In addition to growth retardation, irritability, changes in mental status, and significant edema, patients with kwashiorkor develop a blanching erythema and a red-brown scale with a raised edge resembling "flaky paint." Other features may include depigmentation of the hair, dyschromia, and hypopigmentation of the skin. Kwashiorkor can be confused with acrodermatitis enteropathica, although hypoalbuminemia and edema can be distinguishing features. The condition is reversible after gradual introduction of nutritional therapy, although mortality is quite high if not treated appropriately.[22]

SIGNS OF IMMUNODEFICIENCY

Patients with different immunologic diseases often present with similar initial cutaneous and systemic signs, which raise concern for primary immunodeficiency. Infants with marked immunodeficiency have a clinical phenotype of recurrent infections, erythroderma, diarrhea, and failure to thrive. Many patients manifest with cutaneous abnormalities, some of which are highly characteristic of a particular disorder, whereas others such as erythroderma or eczematous dermatitis may be shared by many **(Table 1)**.

CONCLUSION

Although many neonatal skin diseases are benign, it is important for pediatricians and dermatologists to recognize the subtle signs and symptoms that may provide insight to more serious diseases. Taken together with systemic signs and symptoms, various rashes and lesions may indicate underlying neoplasia, neural tube and spinal dysraphism, nutritional deficiency, or primary immunodeficiency.

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